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EXAMINER	
LYLES, JOHNALYN D	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,747	WOOD ET AL.	
	Examiner	Art Unit	
	Johnalyn Lyles	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *46-69* is/are pending in the application.

4a) Of the above claim(s) *61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *46-60, 63-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *46-69* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The Examiner of U.S. Patent application SN 09/701,747 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Lyles, Technology Center 1600, Art Unit 1647.

2. The amendment filed on 04/07/2003 has been entered into the record and has been fully considered. Applicant has canceled claims 1-45. New claims 46-69 have been added and are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. As a result of Applicant's amendment, all objections and rejections, not reiterated herein have been withdrawn by the examiner.

5. Newly submitted claims 61 and 62 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the addition of SEQ ID NOS: 3, 12, and 14 to which the polynucleotide hybridizes under stringent conditions. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims **61 and 62 are withdrawn from consideration** as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

Claim 47 is objected to because of the following informalities: missing punctuation at the end of the sentence. **Appropriate correction is required.**

Applicant is advised that should claim 47 be found allowable, claim 51 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, there is no change in scope between claims 47 and 51. Claim 51 provides a recitation of use. There is no end output identified or linked to any effect or change such that the method of claim 46 can be used in screening. **Traversal should include the difference in scope between claims 47 and 51.**

Claims 51, 67 and 69 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 51 does not further limit claim 46 as noted above. Claim 51 is merely a recitation of use but does not set forth any additional steps involved in the method/process such that it further limits claim 46 or describes how this use is actually practiced or specifically, when the method identifies the substances as potential analgesics; neuromodulatory agents; anti-inflammatory agents and agents that regulate neurotransmitter release or neuronal excitability.

Claim 67 and 69 do not further limit the preceding claims. Host cells containing the heterologous nucleic acid or protein as claimed, respectively do not further limit the preceding claims. There is no antecedent basis; if applicant wishes to further limit the preceding claim, use terms with proper antecedent basis.

Claim Rejections-Maintained

Claim Rejections - 35 USC §§ 101 and 112, first paragraph

Claims 46-69 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well-established utility or a specific and substantial asserted utility.

The claims are directed to an isolated protein and variants corresponding to SEQ ID NO: 2, referred to in the specification as SPASIC, a nucleic acid corresponding to SEQ ID NO: 1 and variants encoding said SPASIC or variants including alleles and pseudo-alleles, or the degenerative equivalents of the nucleic acid, and the vector and host cells for expression in a eukaryotic cell, and a method for identifying a substance that has ion-channel modulating activity. The instant specification and drawings discloses (see page 2, lines 9-15) that SPASIC is an H^+-gated ion channel and that the nucleic acid (SEQ ID NO: 1) encodes the SPASIC protein (SEQ ID NO: 2). Further, the specification discloses:

1) the transcript is present in the dorsal root ganglion neurons and CNS tissues (page 2, line 20),

2) said SPASIC mediates both a transient and sustained flow of current when exposed to extracellular acidity that is unique to this protein (pg 2, line 22), and

3) shares a 43% sequence identity with ASIC and similarities with ASIC-type proteins (pg 2, line 26).

The specification suggests that because SPASIC is expressed in sensory neurons and because proton-gated channels are important in pain and inflammation (pg 3, line 4-5) that SPASIC is an analgesic drug target. The specification states "No H^+-gated channel having these properties [both a transient and sustained flow of current] has been characterized before" (pg 2, line 31-32). Further, it is suggested that the presence of the protein in subsets of central nervous system neurons suggests an important role as a receptor or autoreceptor involved in the regulation of neurotransmitter release or neuronal excitability or excitotoxicity (Spec. pg 3, line 11-14).

Applicant's arguments filed 4/7/03 have been fully considered but are not persuasive.

Because the specification does not disclose or provide any evidence nor is there any art of record that points to an activity for the nucleic acid or the encoded protein, such that a non-asserted utility would be well-established it is a totally new, uncharacterized protein with ***no well-established utility.***

The specification generally asserts that all of the disclosed SPASIC proteins will be useful for screening assays for analgesic and anti-inflammatory agents; however, the asserted uses do not meet the requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be specific and substantial. The specification asserts:

1) SPASIC is an analgesic drug target useful in screening techniques for identifying novel analgesic and anti-inflammatory agents (Spec. pg 3, line3-6): Applicant argues that pain and inflammation are "specific" conditions and that screening methods to identify agents which

have a "substantial utility" also have a 'real world' context of use." This asserted utility is not specific or substantial. The specification does not disclose nor does the prior art provide the function of SPASIC or any disease states directly associated with the proteins dysfunction. There is no evidence of agents that would inhibit or activate ion channel activity and treat pain and inflammation. Thus, the asserted utility is ***not specific or substantial*** for treatment of the asserted medical conditions, as the agents have no specific or substantial utility and there is no established nexus between SPASIC and any disease associated with pain and inflammation.

Although acidosis accompanies painful inflammatory and ischaemic conditions, and is thought to be mediated by H^+-gated ions channels, other ion channels may be involved. Many ion channels are thought to be involved in pain (McCleskey and Gold, *Annu. Rev. Physiol.* 61:835-56, 1999) and may signal acidosis, including ASICS, TRPV1, ATP-receptors, and GIRKs (Jones *et. al.*, *J. Neurosci.* 24:10974-10979, 2004). Furthermore, BNC1 (ASIC2), a H^+-gated ion channel, was thought to play a role in pH sensing, however, the acid-evoked current in cultured sensory neurons and the response of acid-stimulated nociceptors were normal in BNC1 null mice (Price *et. al. Nature* 407:1007-1011, 2000). Thus, the asserted utility is ***not specific or substantial*** for treatment of the asserted medical conditions.

Although the data in Figure 2 show that SPASIC affects an inward current in response to reducing pH, there are no controls and no evidence that SPASIC is an H^+-gated cation channel responsible for part or all of the activity or that it mediates pain caused by acidosis in sensory neurons. Figure 2 shows only the inward current at pH 5.0. What is the pH dependence/ required pH fluxuation for activation, does amiloride or any other inhibitor block this current, what is the indication of Na+ or ion selectivity? Sensory neurons express several such currents,

which differ in their rate of activation and desensitization. For example, the vanilloid receptor (VR-1), a channel gated by heat and also protons, was thought to be responsible for the acid-activated currents in a population of small neurons from DRG (Tominaga *et al. Neuron* 3:531-543,1998). ASIC2 is an H^+-gated ion channel; however, Price *et. al.* showed reduced mechanosensation and no obvious defects in pain sensation in ASIC2 knockout mice (*Nature* 407:1007-1011, 2000). Thus, all H^+-gated ion channels may not mediate acid-responsive pain in sensory neurons.

To date, the acid-sensing channels or combination of channels responsible for the acid-evoked current in sensory neurons is unknown (Jones *et. al., J. Neurosci.* 24:10974-10979, 2004). Current studies suggest that a combination of two or more degenerin/epithelial sodium channel subunits may coassemble as heteromultimers to generate transient H^+-gated currents in mouse dorsal root ganglion neurons (Benson *et. al. PNAS* 99:2338-2343, 2002). This suggests that understanding how the subunits assemble to form H^+-gated ion channels is critical to understanding channel ***function*** and regulation, and for the development of molecules to ***modulate channel activity***.

The mere presence of the protein in sensory neurons does not indicate the proteins involvement or importance in pain and inflammation management. The assertion that the pain caused by acidosis is mediated by H^+-gated cation channels in sensory neurons, does not provide evidence SPASIC is an H^+-gated ion channel in which agents that block the channel thereby inhibit H^+-gated ion channel thus reducing the pain caused by acidosis in various medical conditions for the reasons noted above regarding uncertainty of what channels are responsible for acid-evoked currents and the idea that all H^+-gated cation channels are not involved in pain.

Applicant argues sequence analysis (Figure 1) and experimental data (Figure 2 and Example 5) of SPASIC's H^+-gated cation channel activity, demonstrate SPASIC mediates the permeability of cations across a membrane in response to low pH; therefore, it is an H^+-gated cation channel responsible for part or all of the H^+-gated cation channel activity which mediates acid responsive pain. Applicant asserts that SPASIC protein described in the specification is not an anonymous, uncharacterized sensory neuron protein and the activity of SPASIC is not simply a matter of prediction. Applicant further asserts that SPASIC is characterized by its expression in sensory neurons and demonstration as a proton-gated channel and absent evidence to the contrary, the ordinary skilled person would understand SPASIC mediates pain, given the knowledge that pain and inflammation are associated with proton-gated channel activity in sensory neurons. However, no such evidence is provided in the disclosure. The specification only discloses on page 1, line 13-14, that the pain is ***thought*** to be mediated by H^+-gated ion channels, while the current status of the art teaches numerous ion channels are involved in pain and specific blockers of H^+-gated ion channels are necessary to study the role these channels in pain since all are not involved in pain.

While Applicants arguments were fully considered, they are not found persuasive in that SPASIC is a characterized protein demonstrated to be physiologically responsible for all or part of the H+ gated cation channel activity, which may mediate acid responsive pain for reasons noted above, in the examples of the vanilloid receptor, which is both heat and proton gated and associated with pain and ASIC2, an H^+-gated ion channel, which does not mediate pain.

Furthermore, structural homology and expression patterns are not always indicators of functional homology; even members in a conserved gene family may show divergent expression

and function. The Na^+ channel/degenerin family shows widespread and overlapping expression and a shared structure; however, they demonstrate a variety of functions. There is no evidence of the function of SPASIC as noted on page 2, lines 9-27, which discloses that SPASIC is present in the spinal cord and throughout the CNS, the transcript is present in dorsal root ganglion neurons and CNS tissue, and that when expressed in transfected COS cells mediates a transient and sustained flow of current when exposed to extracellular acidity.

Expression of the SPASIC transcript in sensory neurons does not necessarily predict that it is important in management of pain and inflammation or that is an analgesic drug target. Many proteins are found in sensory neurons; all are not important in management of pain and inflammation or analgesic drug targets. The specification does not disclose a link between the activity of the protein and a disease that would benefit from the use of agents determined from the screening assay. The function of SPASIC is unknown for the reasons mentioned above. Thus, further undue experimentation would be required to establish a nexus and use the protein in treating these medical conditions.

In addition, increased transcription does not always correlate with increased protein levels. See Haynes *et al.* (*Electrophoresis* 19:1862-1871, 1998), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes *et al.* concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that increased transcription results in increased protein levels.

And, while, as Applicant asserts, all members of the small subset of ion channels, which are proton-gated cation channels from sensory neurons may show similar characteristics and a common activity in directing the passage of cations across the membrane in response to low pH, this does not indicate the channels share the ***same function***. For example, within the ASIC subfamily or subset of the Epithelial Sodium Channel/Degenerin family, there are shared properties, including opening in response to drop in pH below 7.0, Na^+ selectivity, and expression in sensory neurons (McCleskey and Gold. *Annu. Rev. Physiol.* 61:835-56, 1999); and similar structure, including two transmembrane domains (TM1 and TM2), a large extracellular loop, and the C and N termini facing the intracellular space. However, they are functionally diverse; ASICs are important for mechanoreception and nociception at the periphery. For example, ASIC1 is involved in visceral mechanoreceptor function and prolonged gastric emptying of a meal was demonstrated in ASIC1-/- animals (Page *et. al. Gastroenterology*, 127:1739-47, 2004); BNC1 (ASIC2) functions in mechanoperception, as ASIC2 knockout mice showed reduced mechanosensation and no obvious defects in pain sensation; and knockout of ASIC3 led to reduced sensitivity of noxious mechanoreceptors and noxious heat and acid per se and increased sensitivity to the rapidly adapting mechanoreceptors (Krishtal. *Trends in Neurosci.* 26:477-83, 2003).

In addition, while Applicant argues that the channel shares a common mode of action with other known proton-gated cation channels, in mediating an influx of cations across the cell membrane in response to reduced pH, the specification does not disclose that SPASIC has properties identical to ASIC or any other protein, nor that it is a member of the amiloride-sensitive Na^+ channel/degenerin family. Since the specification discloses no H^+-gated channel

having the properties of SPASIC has been characterized (pg 2, line 31-32), the properties of SPASIC cannot be predicted by sequence analysis or comparison to any known H^+-gated ion channels.

Furthermore, the specification does not disclose any secondary or tertiary structural features of the SPASIC protein or any other specific information regarding SPASIC protein such as subcellular location of the protein, pH for activation, ligands, ion selectivity, and physiological significance or functional role SPASIC plays. Therefore, the protein is a new, uncharacterized protein whose function is unknown.

Since one skilled in the art would need to determine a role for SPASIC in the management of pain and inflammation to use the invention, undue experimentation would be required to use SPASIC as a target for analgesic drugs and to use the protein to screen for new analgesic and anti-inflammatory agents for all of the reasons noted above. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is ***not substantial***.

2) SPASIC can be used in screening for agents that regulate neurotransmitter release or neuronal excitability: This asserted utility is not substantial. Since the specification does not disclose the function of SPASIC or any disease states associated with the proteins dysfunction, further experimentation would be required to determine the role of SPASIC in regulation of neurotransmitter release and neuronal excitability. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

3) *the disclosed nucleic acids can be used for preparation of probes and primers for use in hybridizations and PCR amplifications, production of proteins, which can be used in*

production of antibodies and mRNAs encoded by said gene and related nucleic acids, anti-sense technology and use in gene therapy, preparation of medicaments, and preparing "knock-out" mammals. Such utilities do not appear to be either specific or substantial because these uses merely rely on the inherent properties of any nucleic acid to bind and encode. Thus, the disclosed nucleic acids merely constitute research reagents for further experimentation to discover a "real-world" use of the nucleic acids.

Thus, the proposed uses of the SPASIC proteins in screening methods to identify novel analgesic agents and agents that regulate *neurotransmitter release or neuronal excitability and the use of the nucleic acid that encodes SPASIC to produce the protein* are simply starting points for further research and investigation into potential practical uses of the proteins. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 46-69 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's argument that consideration of the Wands factors shows any experimentation required by the ordinarily skilled person in working the invention is not undue experimentation. This is not persuasive for the reasons noted above. Specifically, the polypeptides covered by the

present claims are not functionally defined; thus, the nature of the invention is not such that one of ordinary skill in the art can use the invention. The unpredictability of the art is also such that variants with structural limitations set out in the claims are likely to possess other activity than the stated activity as referenced in the examples given above, including in comparison with ASICs. Since the function of the SPASIC protein is not established, a large quantity of experimentation is necessary to identify polypeptides with the structural and functional features necessary to use the screening method. The lack of direction/guidance presented in the specification regarding a correlation between the activity of the protein and a disease that would benefit from the agents, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which established the unpredictability of pH, acidosis, and acid-sensing ion channel activation in pain and inflammation, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First paragraph

If utility should be found, the following claims are also rejected under 35 U.S.C. 112, first paragraph. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples,

the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims.

Claims 57 and 59-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement** requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the instant case, if utility should be found, claim 57 is not enabled for a nucleic acid according to claim 55, which hybridizes with the complement of the nucleic acid of SEQ ID NO: 1 under high stringency conditions. Hybridizing is not a function of encoding. Many of the polypeptides, encoded by the nucleic acids, which hybridize to SEQ ID NO: 1 are unrelated to the SPASIC of the instant invention. Furthermore, the nucleic acid, which hybridizes to the complement of SEQ ID NO: 1 would encode other, inactive proteins. Unrelated polypeptides isolated by hybridization may be produced by a frameshift in the coding sequence, for example. Due to the large quantity of experimentation necessary to identify the polypeptides with structural and functional features of the instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of altering the structure and function of the protein, and the breadth of the claims which fail to recite structural and functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, the specification does not reasonably provide enablement for the scope of use of short sequences comprising specific sequences of SEQ ID NO: 1. Said sequences may not

be specific for the polynucleotide of SEQ ID NO: 2. The specification has not disclosed how to use said non-specific sequences. In the instant case, claims 59 and 60 are not enabled for use of the short segments of SEQ ID NO: 1 as recited in the claims. Specifically, an isolated nucleic acid molecule comprising a contiguous polynucleotide sequence of at least 16 bases of SEQ ID NO: 1 or the complement of SEQ ID NO: 1 or at least 30 bases of SEQ ID NO: 1 or the complement of SEQ ID NO: 1 lacks enablement. Applicants claims are directed to short segments of at least 16 or at least 30 bases of SEQ ID NO: 1. The specification does not enable the broad scope of the claims which encompasses a multitude of short segments of SEQ ID NO: 1 because the specification does not teach which bases are required such that requisite functionality is maintained, note the utility rejection above. The specification provides essentially no guidance as to which of the possible sequences is likely to be successful in any particular use. Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed short sequences in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

Claims 66-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expression of SPASIC in isolated COS cells, does not reasonably

provide enablement for all multicellular organisms, transgenic organisms or for use in gene therapy. The specification speaks of *in vitro* as *in vivo* assays; and contemplates use of transgenic animals and methods of gene therapy whereby cells are manipulated for expression of heterologous nucleic acid sequences or SPASIC or variants with altered activity within such cells and whole animal organisms, including humans and for use in preparation of a medicament for use in gene therapy.

While the specification is enabling for contact with isolated cells, and the transformation or transfection of isolated cells to express SPASIC via nucleic acid and vector delivery, the specification fails to teach suitable administration such that any suitably transgenic, transformed or gene vector therapy administered organism may be suitably screened. What is lacking is a description of the proper construct and transformation or transfection procedures, as well as mechanisms for assessing SPASIC activation in vivo, including in humans and in transgenics as encompassed by the claims. Those skilled in the art recognize that such technology is currently beyond scope. In particular, Marshall "Gene Therapy's Growing Pains". Science, Vol. 269 (1995), pp. 1050-1055, Orkin et al. "Report and recommendations of the panel to assess the NIH investment in research on gene therapy". (1995). pp. 1-25, and Verma, I. M., et al. "Gene therapy-promises, problems, and prospects". Nature, Vol. 389 (September 1997), pp. 239-242, each denote significant troubles associated with transgenic and in vivo gene therapy approaches to the assessment of in vivo methods and treatments. The specification fails to provide any exemplary evidence for conducting such screening approaches in vivo, using either transgenic or gene therapy treated cells within an organism. Since the scope of "cell" is deemed to be so inclusive as provided by direct guidance within the specification, the scope of enablement

provided by the specification is not commensurate in scope with the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

Claims 46, 48, 52, and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Adding "changes in proton gated cation channel activity" recited in claim 46; "H+ stimulus" recited in claim 48 and 54; and "H^+-gated cation channel activity" recited in claim 52 represents a departure from the specification and claims as originally filed. The new matter introduced does not appear in the specification. If appropriate, support or antecedent basis for new matter that is "new terminology" should be provided to avoid a confusing variety of terms for the same thing.

The claims are drawn to nucleic acid (SEQ ID N0:1) encoding the cation channel SPASIC polypeptide (SEQ ID NO:2), variants thereof (at least 90% sequence identity), fragments of the nucleic acid of SEQ ID NO: 1, using hybridization, producing derivatives of SPASIC protein and nucleic acid encoding SPASIC protein, vectors comprising SPASIC nucleic

acid, a cell containing said vector, method for identifying substance with ion-channel modulating activity using a SPASIC protein and said cell.

The claims, as written, encompass polypeptides, which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2 does not adequately describe the scope of the use of the claimed genus of polypeptides, which encompasses a substantial variety of subgenera including full-length proteins/nucleic acids, chimeric proteins/nucleic acids, fusion proteins/nucleic acids, allelic variants, and variants. The variants (with no known or disclosed function) can be encoded by nucleic acids which hybridize to the polynucleotide of SEQ ID NO:1. The polypeptides, encoded by the polynucleotides isolated by hybridization to the nucleic acid of SEQ ID NO: 1, may be completely unrelated to the polypeptide of SEQ ID NO: 1. Further, polypeptides, comprising fragments and variants of SEQ ID NO: 2, may also, be completely unrelated to the polypeptide of SEQ ID NO: 2. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Regents of the University of Calfornia v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions, which are critical to the structure and function of the genus claimed. The common function of the claimed genus of polynucleotides, which is based upon a common property or critical technical feature of

the genus, which is claimed is not disclosed. Therefore, only the use of isolated polypeptide shown in SEQ ID NO: 2 encoded by DNA molecule comprising a DNA sequence consisting of nucleotides of SEQ ID NO: 1, but not the full breadth of the claims meets the written description provision of 35 USC 1 12, first paragraph.

Claims 46 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, claim 46 is a method for identifying a substance having ion channel modulating activity by measuring changes in the proton-gated activity in response to an interaction between SPASIC and a substance. However, the written description does not teach or provide a description of specific examples of "ion-channel modulating activity." Specifically, the specification does not teach the ability of SPASIC proteins to interact with a substance and modulate ion channel activity. No function of SPASIC or no end output linked to any effect is delineated and no SPASIC proteins providing such interaction that modulates ion channel activity are described.

Claim Rejections - 35 USC § 112, Second paragraph

Claim 46, 47-51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 is indefinite and confusing in that it recites a method for identifying a substance having ion-channel modulating activity. The term "ion channel modulating activity" in claim 46 is a relative term, which renders the claim indefinite because it is not clear what activity is modulated. The specification on page 19, line 25-26 and 29-30 contemplates increasing and reducing the ion channel activity. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of activity of the ion channel, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

Claims 47-51 are rejected for depending upon an indefinite base claim and fail to resolve the issues raised above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Johnalyn Lyles whose telephone number is 571-272-3433. The examiner can normally be reached on M-F 8 am - 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

jdl

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1-6-04